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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/630,333	BURMAN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 21-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-9* is/are allowed.

6)☒ Claim(s) *1,10-14 and 31-50* is/are rejected.

7)☒ Claim(s) *12,13 and 21-50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on July 1, 2003 (Paper No. 17) under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-14 and 21-50 are pending.

Applicants' amendment filed on July 1, 2003 (Paper No. 18) and the Declaration of Inventor, Rama Mukherjee filed April 30, 2003 are acknowledged. Applicants' response and the Declaration of Rama Mukherjee have been fully considered. Claims 1 and 12-14 have been amended, and new claims 21-50 have been added. Therefore, claims 1-14 and 21-50 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 1-12, under 35 U.S.C.112, first and second paragraphs, is withdrawn in view of applicants' amendment the claim and applicants' response at page 2 in Paper No. 18.

Claim Objections

3. Claims 12 and 13 are objected to because of the use of the term "comprising peptide according to claim 1" or "administering of an effective amount of a peptide according to claim 1". Use of "comprising the peptide according to claim 1" for claim 2, and "administering an effective amount of the peptide according to claim 1" for claim 3 are suggested. See also claims 21-40.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1, 12, 13, 31 and 41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 8, 11-14, 17, 18, 20 22-24, 63, 64, 67, 68, 70, 72-74, 327 and 328 of copending application No. 09/896,903. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 12, 13, 31 and 41 in the instant application discloses a peptide of X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2, where X can be butanoyl, R1 can be Trp, R2 can be Ala, R3 can be Aib, and R4 can be Leu; a composition comprising the peptide; and a method of treating cancer of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering the peptide. This is obvious in view of claims 1, 2, 5, 6, 8, 11-14, 17, 18, 20 22-24, 63, 64, 67, 68, 70, 72-74, 327 and 328 of copending application which discloses a pharmaceutical composition comprising at least two peptides selected from SEQ ID NOs: 1-3 and 4, wherein SEQ ID NO:2 is butanoyl-D-Phe-Gln-Trp-Ala-Val-Aib-His-Leu-NH_2, a method of killing or inhibiting the multiplication of tumor cells or a method of treating cancer in human or other animal,

comprising administering at least two peptides selected from SEQ ID NO:1-3 and 4. Both the claims of instant application and the claims of the copending application are directed to a composition comprising the peptide of butanoyl-D-Phe-Gln-Trp-Ala-Val-Aib-His-Leu-NH_2; and a method of treating cancer of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering the peptide. Thus, claims 1, 12, 13, 31 and 41 in present application and claims 1, 2, 5, 6, 8, 11-14, 17, 18, 20 22-24, 63, 64, 67, 68, 70, 72-74, 327 and 328 of copending application are obvious variations of a composition comprising the peptide of butanoyl-D-Phe-Gln-Trp-Ala-Val-Aib-His-Leu-NH_2; and a method of treating cancer of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering the peptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13, 14 and 31-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating various human cancer cell lines *in vitro* by administering a peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12, does not reasonably provide enablement a method for treating various cancers of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering a peptide of formula, X-D-Phe-Gln-R1-

R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12 alone, or by adminstering the peptide in combination with a chemotherapeutic agent, where the chemotherapeutic agent is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 13, 14 and 31-50 encompass a method for treating various cancers of colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian, pancreatic, leukemia or glioblastoma in mammals by administering a peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 or of SEQ ID NO:3-11 or 12 alone (claims 13 and 31-40), or adminstering the peptide in combination with a chemotherapeutic agent (claims 14 and 41-50). The specification, however, only discloses cursory conclusions (page 4, lines 6-9; page 8, lines 1-5) without data supporting the findings, which state that the present invention describes the preparation of peptide analogs of bombesin/gastrin releasing peptide (GRP) using constrained amino acids, and the use of the peptide in cancer therapy. There are no indicia that the present application enables the full scope in view of a method treating various cancers using the peptide analogs of bombesin/GRP as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of

the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the treating conditions for treatment of various cancers in mammals and the chemotherapeutic agent used in the combination therapy, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification demonstrates the treatment of various human cancer cell lines with the peptide of formula, X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH_2 in vitro (Examples 12-14). However, there are no working examples indicating the in vivo treatment of various cancers in mammals using the claimed peptide alone or the combination therapy of the peptide and a chemotherapeutic agent.

(3). The state of the prior art and relative skill of those in the art:

The prior art (references shown at pages 1-4 of the specification) indicates analogs of bombesin/GRP have anti-tumor activity in vitro or in vivo, however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the treating conditions such as the dose and the time for the treatment of various cancers in vivo using the claimed peptide alone or the combination of the peptide and a chemotherapeutic agent to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims are directed to a method for treating various cancers in mammals using the claimed peptide alone or the combination of the peptide with a chemotherapeutic agent. Since the specification only indicates using the claimed peptide in the in vitro treatment of various human cell lines, but does not show the treating conditions for the treatment of various cancers in vivo, nor indicates how to extrapolate the in vitro data to in vivo treatment, thus the effect of the peptide alone or the combination therapy in the claimed method is highly unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating various cancers in mammals using the claimed peptide alone or a combination of the peptide with a chemotherapeutic agent. The specification indicates the cytotoxicity of the peptide for in vitro treatment (see Examples 12-14), it does not indicate the in vivo treating conditions such as the amount of the peptide administered and the time required for the treatment, nor demonstrates the in vivo effects of the peptide either used alone or in combination therapy. Moreover, there are no teachings on how to extrapolate the in vitro data to in vivo treatment, and no working examples are provided for in vivo treatment. Since the specification does not provide sufficient teachings on the treating conditions such as the dose and the time, thus, it is necessary to carry out further experimentation to assess the effect of the peptide for in vivo treatment.

(6). Nature of the Invention

The scope of the claim includes a method for treating various cancers in mammals using the claimed peptide alone or a combination of the peptide with a chemotherapeutic agent,

however the specification has not demonstrated the in vivo treatment using the claimed peptide. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the claimed peptide either used alone or in combination therapy in treating various cancers in mammals.

The declaration of Inventor, Rama Mukherjee has been filed April 30, 2003. In the declaration, the effective dose of the peptide (e.g., 0.25 μg/kg BWt to 500 μg/kg BWt) and a pharmaceutical composition comprising the peptide and pharmaceutically acceptable diluents are provided, and an example of treatment of mice having primary tumor cells of colon adenocarvinoma (PTC) xenografts with SEQ ID NO:11 is shown. The example indicates all control (untreated) animals died by day 29 post treatment, and the percentage inhibition of tumor growth caused by SEQ ID NO:11 at 4.25 μg/100 μl twice a day as compared to untreated on day 29 is 53%.

In response, applicants indicate it is a well known to screen compounds for anticancer effects in vitro systems and in vivo animal models; the specification provides in vitro activity against 6 or more lung or breast cancer cell lines does predict xenograft activity against these tumor types (see Examples 12-14); the Declaration of Dr. Rama Musherjee provides the in vivo data, in which SEQ ID NO:11 inhibited the growth of colon adendocarcinoma by 53% (page 8 of the response); to determine the therapeutical dose in vivo, one skilled in the art would be able to follow the methods known in the art (e.g., U. S. Patent 5,565,431), the in vivo doses are decided

based on the in vitro cytotoxicity, general toxicity, and pharmaceutical properties; how the in vivo dose and in vitro dose for SEQ ID NO:11 are correlated; several references provided by applicants indicating the effective dose used for human can be decided by physician based on the findings from cell culture and mouse experiments; and based on the examples in the application, the data presented in the declaration, and the references provided with this response, applicants conclude claims 13-14 and 31-50 are enabled (pages 8-10 of the response). The response and the declaration have been fully considered, however, the argument is not found persuasive because the in vivo data shown in the declaration only indicates a specific peptide, SEQ ID NO:11 out of 60+ peptides (2 x 3 x 5 x 2 = 60) has some anti-tumor activity toward an animal model having a specific tumor, there are no data indicating the in vivo treatment of animal models having different tumors with different peptides, which is encompassed by the claims, nor provides any teachings where the in vivo effect can be predicted from the in vitro data. Although applicants explain how the in vivo dose used for SEQ ID NO:11 are correlated to the in vitro dose in the xenograft model, it appears the in vivo effect cannot be predicted from the in vitro data. Furthermore, there is no teachings regarding the use and the effect of the peptide and a specific chemotherapeutic compound in the combination therapy either in vitro or in vivo. Regarding the determination of a starting dose in humans from animal data, the references do provide allometric conversions of animal to humans. Since the specification and the declaration have not provided sufficient teachings for in vivo treatment of various cancers using the claimed peptides in the animal models, it is necessary to have further experimentation to assess the effects of the peptides in the treatment of various cancers in mammals.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10, 11, 13, 14 and 31-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 10 and 11 recite the limitation "R3 is Alb" in line 2. There is insufficient antecedent basis for this limitation in the claim.

8. Claims 13, 14 and 31-50 are indefinite because the claim lacks essential steps in the method of treating cancer in mammals. The omitted step is the outcome of the treatment. Claims 14 and 31-50 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

Conclusions

9. Claims 1, 10-14 and 31-50 are rejected, and claims 12, 13 and 21-50 are objected to. It appears claims 2-9 are free of prior art and allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

***

August 16, 2003

CHRISTOPHER S. F. LOW
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